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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,738	07/20/2001	Jonathan Gressel	01/22289	8901

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G E Ehrlich 1995
Anthony Castorina
Suite 207
2001 Jefferson David Highway
Arlington, VA 22202

EXAMINER
KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
1638	9

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/889,738	GRESSEL ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication app ars on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *48-61 and 82-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-47 and 62-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-41 and 62-81, in Paper No. 8 is acknowledged.

Claim Objections

Claim 40 line 2, "port" should be replaced with --part--.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-47 and 62-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims an isolated polynucleotide with sequence identity to SEQ ID NO: 20 having 50-100% sequence identity encoding either a sense molecule capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an active part thereof, or an antisense RNA molecule capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or a functional part thereof;

a polynucleotide encoding a polypeptide having 50-100% sequence identity to SEQ ID NO: 21 having a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase catalytic activity or a functional part thereof;

a nucleotide sequence hybridizable to SEQ ID NO: 20 or a functional part thereof, or an active part thereof, under a range of hybridization conditions from mild to stringent;

a nucleotide sequence encoding either a sense RNA molecule capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

a nucleotide sequence encoding either a sense RNA molecule of SEQ ID NO: 20 or an active part thereof longer than 15 nucleotides capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule of SEQ ID NO: 20 or a portion thereof, longer than 15 nucleotides capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

a nucleotide sequence encoding either a sense RNA molecule having 80-100% sequence identity to SEQ ID NO: 20 or an active part thereof longer than 15 nucleotides capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule having 80-100% sequence identity to SEQ ID NO: 20 or portion thereof longer than 15 nucleotides capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

an isolated nucleotide sequence that is hybridizable to SEQ ID NO: 20 or an active or functional portion thereof, or an active or functional portion thereof longer than 15 nucleotides, under a range of hybridization conditions ranging from mild to stringent; and

an isolated polynucleotide from *Citrus* encoding a polypeptide having a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase catalytic activity.

Applicant describes an isolated polynucleotide of SEQ ID NO: 20 from pomelo encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase of SEQ ID NO: 21.

Applicant does not describe any other polynucleotide encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase from any species other than pomelo, or any polynucleotide sequence encoding a polypeptide having between 50-100% sequence identity to SEQ ID NO: 21, or any nucleotide sequence having 50-100% sequence identity to SEQ ID NO: 20 or any functional or active parts thereof other than SEQ ID NO: 20, or any nucleotide sequence encoding or expressing an RNA molecule that will *in vivo* base pair with, or *in vitro* hybridize to SEQ ID NO: 20 or any other naturally occurring polynucleotide sequence encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Given the failure of the polynucleotide encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or fragments or active parts thereof to be adequately described, cells and plants transformed with said DNA are also inadequately described. See Written Description Guidelines, Federal Register Vol. 66 No. 4, Friday January 5, 2001 "Notices", pages 1099-111.

3. Claims 1-47 and 62-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant broadly claims an isolated polynucleotide with sequence identity to SEQ ID NO: 20 having 50-100% sequence identity encoding either a sense molecule capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an active part thereof, or an antisense RNA molecule capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or a functional part thereof;

a polynucleotide encoding a polypeptide having 50-100% sequence identity to SEQ ID NO: 21 having a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase catalytic activity or a functional part thereof;

a nucleotide sequence hybridizable to SEQ ID NO: 20 or a functional part thereof, or an active part thereof, under a range of hybridization conditions from mild to stringent;

a nucleotide sequence encoding either a sense RNA molecule capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

a nucleotide sequence encoding either a sense RNA molecule of SEQ ID NO: 20 or an active part thereof longer than 15 nucleotides capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule of SEQ ID NO: 20 or a portion thereof, longer than 15 nucleotides capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

a nucleotide sequence encoding either a sense RNA molecule having 80-100% sequence identity to SEQ ID NO: 20 or an active part thereof longer than 15 nucleotides capable of co-suppression of a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or an antisense RNA molecule having 80-100% sequence identity to SEQ ID NO: 20 or portion thereof longer than 15 nucleotides capable of *in vivo* base pairing with a naturally expressed messenger RNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase;

an isolated nucleotide sequence that is hybridizable to SEQ ID NO: 20 or an active or functional portion thereof, or an active or functional portion thereof longer than 15 nucleotides, under a range of hybridization conditions ranging from mild to stringent;

an isolated polynucleotide from *Citrus* encoding a polypeptide having a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase catalytic activity

and cells and plants transformed therewith.

Applicant teaches the isolation of a polypeptide from pomelo having flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase activity by means of partial peptide sequencing to obtain primers for RT and RACE PCR; isolation of partial cDNA fragments by RT-PCR; isolation of the 5' end of the pomelo cDNA clone encoding flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase; and the polynucleotide of SEQ ID NO: 20 encoding the polypeptide of SEQ ID NO: 21, a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase from pomelo.

Applicant does not teach any nucleotide sequences encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or fragments or active parts thereof other then SEQ ID NO: 20; or plants or cells transformed with SEQ ID NO: 20 or any other nucleotide sequence encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or fragments or active parts thereof.

Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol *et al.* (1999, Plant Molecular Biology 40: 857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2nd paragraph). Fourgoux-Nicol *et al.* also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into

account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Further, when considering the likely reduction in sequence identity or homology of the transgene or transgene fragment to the target gene in closely or distantly related species, uncharacterized with respect to the number of target gene isoforms or the specific degree of sequence identity between the parts of the transgene and orthologus endogenous gene, the phenotypic character or reduction in gene expression expected from expression of a DNA construct often cannot be reliably predicted. In an example that demonstrates this all too common and unpredictable feature in the art, antisense expression of a *gchs2* gene resulted in only partial reduction of *gchs3* and *gchs1* isoforms of the gene in transgenic *Gerbera hybrida* (Elomaa P. *et al.*, Molecular Breeding 1996, 2: 41-50 on page 48, column 2 lines 4-10). This example is analogous to having orthologous transgenes from one species not having an effect upon the endogenous ortholog of a closely related or distantly related target species because of reduced sequence identity. The co-suppression of gene expression is also dependent upon a high degree of sequence identity or homology (Waterhouse P. *et al.*, Trends in Plant Sciences, November 1999, Vol. 4, No. 11 pp. 452-457; page 453 column 1 lines 32-40).

Moreover, the phenotypic character expected from expression of a DNA construct often cannot be reliably predicted. In an example that demonstrates this all too common and unpredictable feature in the art, antisense expression of a polygalacturonase gene in transgenic tomato had no effect on fruit softening (Smith C. *et al.*; Nature 1988, 334: 724-726, p. 725).

Given the lack of guidance for isolating any other nucleotides encoding flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or for producing plants transformed with varied lengths

or varied degrees of sequence identity of a nucleotide of SEQ ID NO: 20 in sense or antisense orientation or any other non-exemplified nucleotide sequences encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase in either sense or antisense orientation or fragments or active parts thereof, the breadth of the claims, and given the unpredictability in the art, undue trail and error experimentation would be needed by one skilled in the art to isolate a multitude of non-exemplified nucleotide sequences encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase, or to evaluate the ability of a multitude of non-exemplified nucleotide sequences encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or non-exemplified fragments to reduce expression of nucleotide sequences encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase in a multitude of non-exemplified transformed plant species. Therefore, the invention is not enabled.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10, 21, 31, 41, 69, and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims fail to recite the amount of time for the hybridizations and wash steps.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The claims are broad for the reasons discussed supra. In particular, the claims are drawn to a polynucleotide encoding an antisense RNA molecule capable of *in* vivo base pairing to a naturally expressed mRNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase; a p0olynucleotide encoding an RNA molecule capable of co-suppressing a naturally expressed RNA that encodes a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase; a portion of SEQ ID NO: 20 longer than 15 nucleotides; a portion of a nucleotide sequence having 80-100% sequence identity to SEQ ID NO: 20 longer than 15 nucleotides; a portion of a nucleotide sequence longer than 15 nucleotides and hybridizable to SEQ ID NO: 20 under mild, moderate, or stringent conditions; an active part of a nucleotide having 50-100% sequence identity to SEQ ID NO: 20; an active part of a nucleotide sequence that hybridizes to SEQ ID NO: 20 under mild, moderate, or stringent conditions; and an active part of SEQ ID NO: 20.

8. Claims 14-18, 20-21, 24-28, 30-31, 62-69, and 72-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luth D. *et al.* Plant, Cell, Tissue and Organ Culture, 57 (3): 219-222, in view of Mok D. *et al.*, GenBank Accession No. AF101972, submitted October 26, 1998 and Bar-Peled M. *et al.*, J. of Biol. Chem., 1991 November 5, Vol. 266, No. 31, pp. 20953-20959.

Luth teaches transformation of grapefruit (see, e.g., page 20953, Abstract).

Mok teaches isolation of a polynucleotide encoding an antisense RNA molecule capable of *in* vivo base pairing to a naturally expressed mRNA encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase; a polynucleotide encoding an RNA molecule capable of co-suppressing a naturally expressed RNA that encodes a flavanone-7-O-glucoside-2"-O-

rhamnosyl-transferase; a portion of SEQ ID NO: 20 longer than 15 nucleotides; a portion of a nucleotide sequence having 80-100% sequence identity to SEQ ID NO: 20 longer than 15 nucleotides; a portion of a nucleotide sequence longer than 15 nucleotides and hybridizable to SEQ ID NO: 20 under mild, moderate, or stringent conditions; an active part of a nucleotide having 50-100% sequence identity to SEQ ID NO: 20; an active part of a nucleotide sequence that hybridizes to SEQ ID NO: 20 under mild, moderate, or stringent conditions; and an active part of SEQ ID NO: 20 (See GenBank document and attached sequence report, Result No. 15).

Bar-Peled teaches the isolation of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase activity from pomelo, its role in the flavor of grapefruit, and the usefulness of genetic engineering to modify flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase activity (see, e.g., page 20953, Abstract).

It would have been *prima facie* obvious at the time of Applicant's invention to modify the invention of Luth to substitute a nucleotide sequence taught by Mok and the utility of modifying bitterness in grapefruit by modifying flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase enzyme activity from pomelo taught by Bar-Peled. One would have been motivated by the teaching of Luth that the method was generally applicable using any nucleotide coding sequence or fragment or portion thereof. One would have had a reasonable expectation of success of modifying the levels of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase enzyme activity of grapefruit in view of the success of Luth. Choice of intra or extra chromosomal integration would have been an optimization of experimental parameters within the skill level of the ordinary artisan.

9. All claims are rejected.

10. Claims 1-13, 19, 22-23, 29, 32-47, 70-71, and 80-81 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest an isolated polynucleotide encoding a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase from pomelo.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Gwendolyn Payne, whose telephone number is (703) 305-2475.

Russell Kallis Ph.D.
November 21, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638